



# Neural correlates of semantic and episodic memory retrieval

Cheri L. Wiggs\*, Jill Weisberg, Alex Martin

*Laboratory of Brain and Cognition National Institute of Mental Health, Bethesda, MD 20892-1366, USA*

Received 1 November 1997; accepted 9 March 1998

## Abstract

To investigate the functional neuroanatomy associated with retrieving semantic and episodic memories, we measured changes in regional cerebral blood flow (rCBF) with positron emission tomography (PET) while subjects generated single word responses to achromatic line drawings of objects. During separate scans, subjects either named each object, retrieved a commonly associated color of each object (semantic condition), or recalled a previously studied uncommon color of each object (episodic condition). Subjects were also scanned while staring at visual noise patterns to provide a low level perceptual baseline. Relative to the low level baseline, all three conditions revealed bilateral activations of posterior regions of the temporal lobes, cerebellum, and left lateralized activations in frontal regions. Retrieving semantic information, as compared to object naming, activated left inferior temporal, left superior parietal, and left frontal cortices. In addition, small regions of right frontal cortex were activated. Retrieving episodic information, as compared to object naming, activated bilateral medial parietal cortex, bilateral retrosplenial cortex, right frontal cortex, thalamus, and cerebellum. Direct comparison of the semantic and episodic conditions revealed bilateral activation in temporal and frontal lobes in the semantic task (left greater than right), and activation in medial parietal cortex, retrosplenial cortex, thalamus, and cerebellum (but not right frontal regions) in the episodic task. These results support the assertion that distinct neural structures mediate semantic and episodic memory retrieval. However, they also raise questions regarding the specific roles of left temporal and right frontal cortices during episodic memory retrieval, in particular. © 1998 Elsevier Science Ltd. All rights reserved.

**Keywords:** PET; Semantic knowledge; Explicit memory; Cued recall; Color

## 1. Introduction

During our lifetimes, we acquire a vast amount of information that we refer to as “stored in memory.” Memories can vary according to several descriptive features, including the relation of the memory to a specific context and mode of retrieval. Tulving [75] differentiated two general types of information stored as semantic and episodic memory. Semantic memory refers to generic knowledge that is context-free (e.g., the name and color of a banana) and, typically, is retrieved automatically. Episodic memory, on the other hand, refers to information that is unique to an individual, is tied to a specific context (e.g., I ate a banana at lunch yesterday), and requires conscious recollection to be retrieved.

Neuropsychological data suggest that these different types of memory may depend on separate (although probably overlapping) cortical structures [62]. Lesion data have shown that, for semantic knowledge, left tem-

poral regions appear to be crucial for storage [e.g., 14, 28, 67] whereas left frontal cortex is implicated in retrieval [e.g., 32, 44], suggesting that accessing semantic knowledge depends on the orchestration of a distributed network of cortical areas. Moreover, despite their impaired semantic knowledge, patients with left temporal lobe damage [14, 68] or left frontal cortical damage [44] have relatively preserved memory for episodic information.

Episodic memory function, on the other hand, is impaired after damage to medial temporal structures (i.e., hippocampus, parahippocampal gyrus, perirhinal cortex, and entorhinal cortex) or to the diencephalon (i.e., dorsomedial nucleus of the thalamus and mamillary bodies). The resultant amnesic syndrome is hallmarked by profound forgetfulness for new information (anterograde amnesia) and for some previously acquired information (retrograde amnesia), but general knowledge retrieval is intact [53]. Although medial temporal and diencephalic structures are important for establishing episodic memories, and may be necessary for retrieval of newly learned information, they are not the site for memory storage [69]. Presumably, episodic memories are stored in neocortex, possibly near or in the same regions involved in perceptual processing of the information [59]. In addition,

\* Corresponding author. Laboratory of Brain and Cognition, National Institute of Mental Health, Building 10, Room 4C104, 10 Center Dr MSC 1366, Bethesda, MD 20892-1366, USA. Tel.: 001 301 435-4928; fax: 001 301 402-6658; e-mail: cheri@codon.nih.gov

neuropsychological evidence suggests that damage to frontal cortex (left or right) can impair specific aspects of episodic mnemonic performance, such as memory search processes and organizational strategies (for reviews, see [65, 82]).

In general, functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) with normal individuals support and extend these neuropsychological findings. As would be predicted by lesion data, subjects performing semantic retrieval tasks show increased regional cerebral blood flow (rCBF), or activations, in left inferior and dorsolateral frontal cortex and left posterior temporal cortex [13, 40, 41, 48]. Moreover, activation in medial temporal structures has been reported during encoding [e.g., 29, 42, 72] and episodic retrieval [e.g., 24, 52, 60]. However, despite the proposal that episodic memories are stored in neocortex, near or in the same regions involved in perceptual processing, surprisingly few functional imaging studies report such activations (although see [47, 61] for exceptions). Instead, the most frequently reported area of activation is in the medial parietal region (i.e., precuneus) [e.g., 8, 16, 26, 33, 64, 77]. Consistent with lesion data, retrieving episodic information activates frontal cortex, but with the surprising caveat that right frontal regions are reliably activated more than the left (see [9, 50] for reviews). It has also been found that the left frontal cortex is differentially more activated during encoding. These general trends in functional imaging data of frontal cortex have lead Tulving and colleagues to propose the Hemispheric Encoding/Retrieval Asymmetry (HERA) model [76].

Interpreting functional imaging data for semantic and episodic tasks is difficult, however, as there are often differences between semantic and episodic tasks besides the nature of the memories. These differences could affect retrieval strategies used by subjects. For instance, Fletcher et al. [16] reported that subjects performed perfectly (100%) in their semantic task, but less accurately (81%) in the episodic task. Different levels of performance can confound the interpretation of differences in brain activity (see [51]). Also, the semantic tasks often used have multiple potentially correct answers (e.g., stem completion asks the subject to complete a three letter stem with the first word that comes to mind) whereas episodic tests have only one correct answer, so search strategies for semantic tests are typically less constrained than for episodic tests (i.e., open ended search vs restricted search).

Although previous PET studies have included semantic and episodic tasks in the same experiment, typically the semantic task is included as a reference, or control, task for the episodic task [7, 16, 64, 71]. The present study, on the other hand, was designed to equate the semantic and episodic tasks as much as possible. We trained subjects to a high criterion performance on the episodic task so

that accuracy levels were matched to those on the semantic and episodic tasks. In both tasks, subjects were asked to retrieve color names for achromatic line drawings. Thus, the stimuli (achromatic line drawings of objects) and responses (names of colors) for both tasks were identical. However, in one condition, color names were retrieved from semantic memory; i.e., general knowledge of an item's typical color (e.g., yellow banana, white igloo). In another condition, color names were retrieved from episodic memory; i.e., specific knowledge from a previous study episode in which the items were visually presented in an uncommon color (e.g., red snowman, green lips).

We chose to study semantic and episodic memory of color for the following reasons: First, within a particular modality (e.g., vision), the particular *attribute* retrieved may affect what areas of the brain are activated [40]. By constraining the particular attribute to be retrieved, we controlled for variation that could be due to processes other than those directly related to memory retrieval. Second, because we have evidence for the neural correlates of semantic memory for color [40] the current study was an opportunity to replicate and expand those findings.

## 2. Methods

### 2.1. Subjects

We tested 16 right handed subjects (equal number of male and female). Their mean age was 27.7 years (range = 21–38) and education was 17 years (range = 12–20). Their mean verbal intelligence score, as estimated by the American version of the Nelson Adult Reading Test [27], was 120 (range = 107–129). Subjects were screened for neurological and psychiatric illnesses and all subjects reported being in good health. Informed consent was obtained in writing from each subject, and all were paid to participate.

### 2.2. Materials

A set of 135 black and white line drawings of objects was selected (most from [66]) with the restriction that all items had typical colors associated with them (e.g., footballs are typically brown, whereas shirts can be a variety of colors). From this set, 90 (6 lists of 15) items were identified as the “unique set” and 45 (3 lists of 15) items were identified as the “fixed set.” (The purpose of the unique and fixed sets will be explained below.) All lists were equated for name frequency [36], categories, category typicality rankings [4], and color association (e.g., number of items which are typically yellow). An additional list of 40 objects were selected to serve as practice stimuli for generating semantic color words dur-

ing the training session. Study books containing 45 line drawings (2 unique sets and 1 fixed set) were created for learning the object-color associations (episodic) during the training session. Each line drawing was colored (e.g., black, lemon) and the written name of the color appeared below the object.

Thirty items were presented during each scan. The fixed set of 15 items occurred in random order at the beginning and at the end of the list (the first 7 and last 8 objects). This set was repeated for each condition (e.g., the same fixed set was presented for both episodic scans). Three different fixed sets were presented across conditions (naming, semantic, and episodic) for each subject. These items served as a buffer to engage subjects in the task and to provide data on consistency of responses to the same objects within and across subjects. The intervening 15 unique items, whose presentation coincided with the PET scan window, were seen by a subject only once during the experimental session (see [40]). These unique item sets were counterbalanced across conditions and subjects. Thus, across subjects, each item was presented in each condition (e.g., responses for igloo were “igloo,” “white,” and “yellow”). However, for a given subject, different items were presented during the scans for naming, semantic retrieval, and episodic retrieval.

An additional set of stimuli (visual noise patterns) were used for the perceptual baseline task, that consisted of randomly ordered black dots on a  $10 \times 10$  cm white background (see [41]). The size of the noise patterns was determined by the area in which the line drawings would be presented.

The experiment was conducted on a Macintosh IIfx computer (Apple, Cupertino, CA) using SuperLab software (Cedrus, Wheaton, MD), which presented the stimuli and recorded subjects' voice on-set times. Stimuli were presented on a computer monitor positioned approximately 60 cm from the subject's eyes and tilted to face the subject. Examples of the stimuli and responses are presented in Fig. 1.

### 2.3. Task procedure

#### 2.3.1. Training session.

Subjects were initially trained between 24 and 48 h before the scans. Subjects first studied a book of 45 colored objects for 10 min. They were then shown achromatic line drawings of these objects on a Macintosh computer, one at a time, and asked to recall the color in which each object had been studied. There was no time constraint for answers and subjects received feedback for each answer. If subjects performed at less than 90% accuracy, they received an additional 5 min of study time and were given the same test. This continued until the subject performed at 90% accuracy or above. The average number of trials to criterion was 1.4 trials.

After completing the memory test, subjects were then

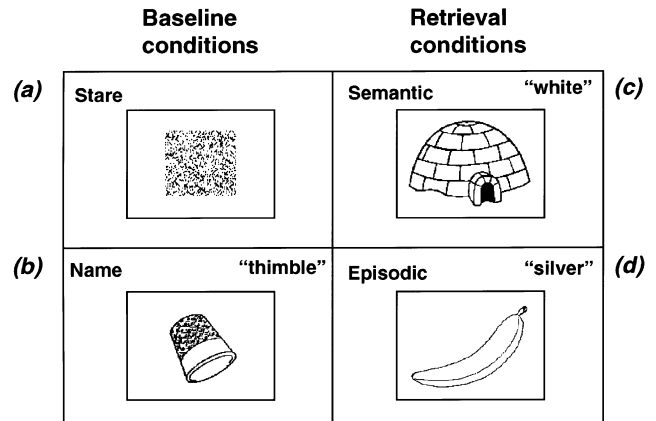


Fig. 1. Examples of stimuli and responses during scanning for (a) low level perceptual baseline (visual noise), (b) object naming baseline, (c) semantic retrieval, and (d) episodic retrieval conditions.

familiarized with the task that would be required during the scanning session. The presentation rate for these training task items was the same as that of the scanning session (described below). First, subjects were asked to name objects. The unique lists from the naming and semantic conditions were presented for this task, to control for the previous exposure of the episodic memory items. Second, subjects were shown a different set of objects only shown during the training session and asked to practice retrieving color names from semantic memory. Third, subjects were given another episodic memory test. All but one subject performed at or above criterion on this final test (this subject was given feedback and an additional test). Subjects also briefly reviewed the episodic memory stimuli an hour before the scans.

#### 2.3.2. Scanning session.

Eight scans were obtained from each subject and each condition was scanned twice. The low level perceptual baseline task was always presented first and last. This first scan was included as an orientation scan for subjects (to control for the novelty of the scanning environment) and was not included in subsequent analyses. The intervening naming, semantic, and episodic conditions were counterbalanced accordingly: each condition was assigned to two blocks (first scan block and second scan block), so that each block comprised all three conditions. The order of conditions within each block was counterbalanced across subjects.

The start time of each task was adjusted to ensure that the unique items were presented during the critical first 20–30 s of the 60-s scan window [31]. For each scan condition, 30 stimuli were presented in the center of a video monitor at the rate of 1 stimulus every 3 s. Each stimulus was presented for 180 ms, followed by a centrally located fixation cross. In the perceptual baseline task, subjects viewed the visual noise patterns and were told

to simply stare at the stimuli. In the other conditions, achromatic line drawings of objects were presented and subjects were instructed to limit their response to a single word (either the object's name, a color normally associated with that object, or the color learned previously for that object). Voice on-set time and error rate were recorded as measures of difficulty and accuracy, respectively. Post experimental interviews were also conducted after the entire scanning session ended to record subjects' subjective experiences during the scans (e.g., the retrieval methods used to recall semantic and episodic information, degree of imagery noted during different conditions, perceived difficulty of task).

#### 2.4. PET scanning procedure

PET scanning was performed with a Scanditronix PC2048-15B tomograph (Milwaukee, WI) which acquired 15 contiguous, 6.5 mm thick cross-sectional images per scan. The resolution was 6.5 mm, full-width at half-maximum (FWHM). A thermoplastic mask was modeled to each subject's head and attached to the scanner bed to minimize head movement. Subjects were positioned within the tomograph so that they could view a computer monitor. A small catheter was placed in the right arm of each subject for subsequent intravenous bolus injections of 37.5 mCi of  $H_2^{15}O$  per scan. Subjects began each task approximately 30 s prior to the injection. Scanning began when the brain radioactivity count reached a threshold value and continued for 60 s. Scans were 10 min apart. As blood flow increases are known to be linear function of radiation counts for scans lasting less than one min [18, 30], local radiation counts were used as an estimate of local blood flow.

#### 2.5. PET data analysis

All scans were first corrected for head movements [37, 45, 49] and task related differences in rCBF were then tested using Statistical Parametric Mapping (SPM) [19–22]. Specifically, each scan was scaled to the dimensions of the Talairach and Tournoux [74] stereotactic atlas brain, aligned to the estimated location of the line connecting the anterior and posterior commissures (AC–PC line), and reshaped to conform to a template PET scan. Each scan was resampled into voxels that were  $2 \times 2 \times 4$  mm in the  $x$ ,  $y$ , and  $z$  planes, respectively, and then smoothed using a gaussian filter with a FWHM of 2 cm in  $x$  and  $y$ , and 1.2 cm in  $z$ . After each individual's scan was resampled into a standard brain coordinate space, statistics were calculated for each voxel sampled in all subjects. The rCBF for each voxel was corrected for variations in global blood flow by dividing each voxel value by the global mean for that scan. The significance of rCBF differences between task conditions was tested by  $t$ -tests, and expressed as standard  $Z$  values.

The PET results are reported in terms of the differences between averaged blood flow patterns yielded by each comparison. We refer to resultant higher blood flow as "activations." The peak locations of significant activations were thresholded for  $Z$  scores greater than or equal to 3.09 ( $P < 0.001$ , one-tailed) and are expressed as coordinates in the Talairach and Tournoux [74] brain atlas. For cortical areas predicted *a priori*, we also report activations thresholded for  $Z$  scores greater than or equal to 2.33 ( $P < 0.01$ , one-tailed).

### 3. Results

#### 3.1. Behavioral data

Response accuracy and voice response time for each condition were recorded. Errors (defined as either perceptual errors, retrieval errors, or failures to respond) were rare: Subjects were able to name 96% of the items, to generate appropriate semantic-based colors for 98% of the items, and to remember episodic-based colors for 97% of the items. Error rates did not differ for the three conditions ( $P > 0.10$ ); thus all conditions were matched on accuracy. There was also good agreement between subjects on the color assigned to each object in the semantic condition (mean proportion of subjects retrieving the same word for the object = 85%). In addition, subjects gave consistent responses to the objects presented on both semantic condition scans (mean response consistency to the fixed set of 15 items = 88%).

Voice onset differed for each of the three conditions ( $F(2, 30) = 91.7$ ,  $P < 0.0001$ ). As we anticipated, naming speed ( $M = 644$  ms,  $SD = 103$ ) was faster than the semantic ( $M = 853$  ms,  $SD = 146$ ) ( $F(1, 30) = 182.4$ ,  $P < 0.0001$ ) and episodic ( $M = 763$  ms,  $SD = 141$ ) ( $F(1, 30) = 34.4$ ,  $P < 0.0001$ ) retrieval conditions. Subjects were also faster retrieving color names from episodic memory than from semantic memory ( $F(1, 30) = 58.4$ ,  $P < 0.0001$ ). These data are from all 30 items presented during each condition (analyses limited to the 15 unique objects presented during each scan did not differ from those reported here).

Post-experimental interviews revealed that subjects, in general, agreed that their retrieval search strategies were similar for both semantic and episodic tasks (specifically, they were aware of retrieving only one answer rather than several answers from which to choose). Subjects varied, however, in their reports regarding the degree of imagery used (specifically, whether the colors were visualized before verbalizing) and the perceived difficulty in the two conditions. Some subjects reported experiencing the same degree of imagery during retrieval in both conditions, whereas others reported more imagery during episodic retrieval or during semantic retrieval. Likewise, some subjects reported the two conditions were equally diffi-

cult, whereas others reported that the semantic condition was more difficult than was the episodic condition (in agreement with the voice onset data, no one noted the episodic condition to be more difficult than the semantic condition).

### 3.2. PET data

Our strategy for analyzing the rCBF data was first to compare each cognitive task (naming, semantic, and episodic) to the same low level baseline condition (the second visual noise scan) (see Table 1a,b,c and Fig. 2). These comparisons were interpreted to indicate activity attributed to general object identification processes, retrieval operations, and speech production as well as the processes specifically associated with each type of cognitive task.

Relative to the low level baseline, the overall pattern of activity associated with each cognitive task was highly similar (see Fig. 2). All three conditions revealed bilateral activations of the medial temporal lobes and the occipito-

temporal region (greater on the left than right). To evaluate how rCBF was modulated in these regions by each task, we selected two left temporal lobe sites that were activated during semantic retrieval relative to the low level baseline, with peak activity in the fusiform gyrus ( $-40, -32, -12$ ) and hippocampal region ( $-24, -36, 0$ ). The rCBF values measured at these pixels were submitted to separate analyses of variance (ANOVAs). Naming, semantic retrieval, and episodic retrieval produced notably higher rCBF values than visual noise in the left fusiform gyrus (see Fig. 3a) (Omnibus  $F(3, 45) = 20.2$ , with planned comparisons showing greater rCBF for naming,  $F(1, 45) = 29.1$ , semantic,  $F(1, 45) = 55.3$ , and episodic,  $F(1, 45) = 10.6$ , than for visual noise, all  $P$ 's  $< 0.005$ ). Semantic retrieval produced the greatest amount of activation (semantic vs naming,  $F(1, 45) = 4.2$ ,  $P < 0.05$ ; and semantic vs episodic,  $F(1, 45) = 17.4$ ,  $P < 0.0001$ ), followed by naming (naming vs episodic,  $F(1, 45) = 4.6$ ,  $P < 0.05$ ). In the hippocampal region, all conditions produced greater rCBF values than visual noise (see Fig. 3b) (Omnibus  $F(3, 45) = 10.2$ , with

Table 1a

Local maxima within areas demonstrating significantly greater rCBF for naming against low level perceptual baseline

Brain regions (Brodmann Area)	Coordinates			Z score
	x	y	z	
<b>Object naming greater than visual noise baseline</b>				
Frontal lobe				
L. inferior frontal gyrus (44)	−38	8	8	5.00
L. insula/claustrium	−30	6	4	4.95
L. precentral gyrus (4)	−46	−14	40	4.74
Medial premotor/Anterior cingulate (6/32)	−4	4	44	4.50
R. precentral gyrus (4)	46	−12	36	3.79
Parietal lobe				
L. postcentral gyrus (43)	−48	−10	20	4.19
Occipital lobe				
L. cuneus (18)	−18	−82	12	3.11
Temporal lobe				
L. inferior temporal gyrus (37)	−38	−56	−20	7.24
L. hippocampal region	−30	−38	4	4.22
L. superior temporal gyrus (22)	−54	−24	4	3.90
R. superior temporal gyrus (22)	46	−12	4	4.18
Subcortical structures				
L. thalamus (ventral posterior lateral nucleus)	−14	−16	8	4.48
R. thalamus (dorsomedial nucleus)	8	−14	8	5.18
R. caudate nucleus	12	8	16	4.73
R. putamen	22	0	8	4.79
	18	8	8	4.68
	28	−6	8	4.79
Cerebellum				
Left	−22	−60	−24	7.55
Midline	4	−65	−24	7.45
Right	22	−52	−24	7.37

Notes: The coordinates are from the atlas of Talairach and Tournoux [74], where x, y, and z correspond to the right-left, anterior-posterior, and superior-inferior dimensions, respectively. Only activations with  $Z > 3.09$  are reported. Brodmann areas are included in parentheses.

Table 1b

Local maxima within areas demonstrating significantly greater rCBF for semantic retrieval against a low level perceptual baseline

Brain regions (Brodmann Area)	Coordinates			Z score
	x	y	z	
Semantic retrieval greater than visual noise baseline				
Frontal lobe				
L. inferior frontal cortex (45)	−40	20	20	5.23
L. insula	−32	12	8	5.91
L. precentral gyrus (4)	−48	−10	44	5.40
	−46	−2	24	4.79
Medial premotor/Anterior cingulate (6/32)	−4	8	44	5.69
R. precentral gyrus (4)	46	−10	44	3.36
Temporal				
L. fusiform gyrus (20)	−40	−32	−12	5.24
L. hippocampal region	−24	−36	0	4.18
R. superior temporal gyrus (22)	48	−26	4	3.14
Subcortical				
L. pulvinar	−4	−24	4	5.14
L. thalamus (dorsomedial nucleus)	−14	−18	8	4.54
R. thalamus (dorsomedial nucleus)	12	−16	8	5.33
R. putamen	18	8	8	4.68
Cerebellum				
Left	−22	−60	−24	7.28
	−38	−56	−20	7.24
Midline	5	−64	−24	> 7.98
Right	22	−52	−24	7.23

Notes: The coordinates are from the atlas of Talairach and Tournoux [74], where *x*, *y*, and *z* correspond to the right–left, anterior–posterior, and superior–inferior dimensions, respectively. Only activations with  $Z > 3.09$  are reported. Brodmann areas are included in parentheses.

planned comparisons showing greater rCBF for naming,  $F(1, 45) = 15.6$ , semantic,  $F(1, 45) = 26.8$ , and episodic,  $F(1, 45) = 15.5$ , than for visual noise, all  $P$ 's  $< 0.0005$ ) but in this region there was no difference between the naming, semantic, and episodic conditions (all  $P$ 's  $> 0.10$ ).

Relative to the low level baseline, each condition was also associated with massive bilateral cerebellar activation, as well as left lateralized activations in the inferior frontal cortex (Brodmann Area, or BA 44/45), primary motor cortex (BA 4), and anterior cingulate region (BA 6/32). Additionally, all conditions activated the right dorsomedial nucleus of the thalamus. Of particular note: none of the tasks produced right prefrontal activation. The main variation in rCBF across the three conditions relative to the low level baseline was that only episodic retrieval was associated with bilateral activation in the posterior parietal region (more on the right than the left) which extended from the lateral superior parietal lobes to medial parietal cortex (see Table 1).

The next baseline comparisons (i.e., semantic minus naming baseline and episodic minus naming baseline) indicated activity that could be attributed to each type of memory task, over that required by naming (see Table 2 and Fig. 4). Retrieving semantic information activated

left frontal cortex (BA 9). Less robust activations ( $Z \geq 2.33$ ,  $P < 0.01$ ) were also found in two right frontal regions (BA 9 and 46). In addition, posterior activations were revealed in left superior parietal cortex (BA 7/19), with weaker activations ( $Z \geq 2.33$ ,  $P < 0.01$ ) in left fusiform gyrus of the temporal lobe (BA 37). Similar to the semantic condition, retrieving episodic information revealed a weak activation ( $Z \geq 2.33$ ,  $P < 0.01$ ) in right frontal cortex (BA 9; unlike the semantic condition, however, BA 46 was not activated). More robust activations were found in lateral posterior parietal cortex bilaterally (BA 7/19), medial parietal cortex (precuneus, BA 7), retrosplenial cortex bilaterally (BA 23), the left and midline cerebellum, and right thalamus.

The areas differentially activated by the two memory retrieval tasks were identified by a third pair of analyses in which the episodic and semantic memory tasks were directly contrasted with each other (see Table 3 and Fig. 5). The areas activated more by the semantic condition than by the episodic condition were in frontal and temporal cortex (much greater on the left than right) (see Fig. 5a). Specifically, semantic retrieval was associated with activation of an extensive region in left inferior and orbitofrontal cortex, with maxima noted in BA 45, 10, and 11, and a less extensive left superior frontal region

Table 1c

Local maxima within areas demonstrating significantly greater rCBF for episodic retrieval against a low level perceptual baseline

Brain regions (Brodmann area)	Coordinates			Z score
	x	y	z	
Episodic retrieval greater than visual noise baseline				
Frontal lobe				
L. middle/inferior frontal cortex (9/45)	−46	20	24	3.37
L. insula	−22	16	12	3.58
L. precentral gyrus (4)	−45	−13	40	4.56
Medial premotor/Anterior cingulate (6/32)	−4	4	44	4.20
Parietal lobe				
L. postcentral gyrus (43)	−52	−8	20	4.21
L. superior parietal cortex (7/19)	−22	−68	32	5.02
R. superior parietal cortex (7/19)	20	−76	36	3.30
R. precuneus/cuneus (7/19)	8	−76	36	3.45
Occipital lobe				
L. fusiform gyrus (18)	−34	−88	−8	3.38
L. lingual gyrus (18)	−8	−72	4	3.78
R. cuneus (18/19)	2	−78	32	3.31
Temporal lobe				
R. superior temporal gyrus (22)	46	−18	4	3.20
Subcortical				
R. thalamus (dorsomedial nucleus)	8	−14	4	6.86
L. putamen	−24	8	8	3.79
R. putamen	19	5	8	5.31
Cerebellum				
Left	−40	−58	−28	> 7.98
Midline	0	−64	−24	> 7.98
Right	14	−60	−24	> 7.98

Notes: The coordinates are from the atlas of Talairach and Tournoux [74], where *x*, *y*, and *z* correspond to the right–left, anterior–posterior, and superior–inferior dimensions, respectively. Only activations with  $Z > 3.09$  are reported. Brodmann areas are included in parentheses.

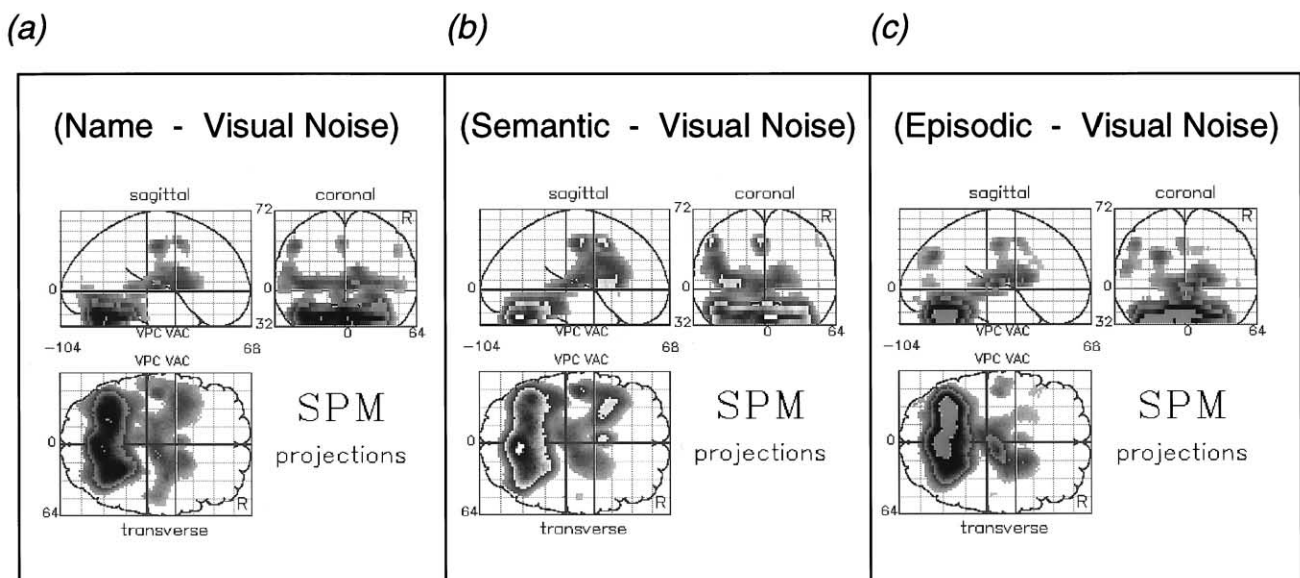


Fig. 2. Regions showing increased blood flow (thresholded to Z-scores  $\geq 3.09$ ) for (a) object naming, (b) semantic retrieval, and (c) episodic retrieval relative to the low level perceptual baseline (visual noise).

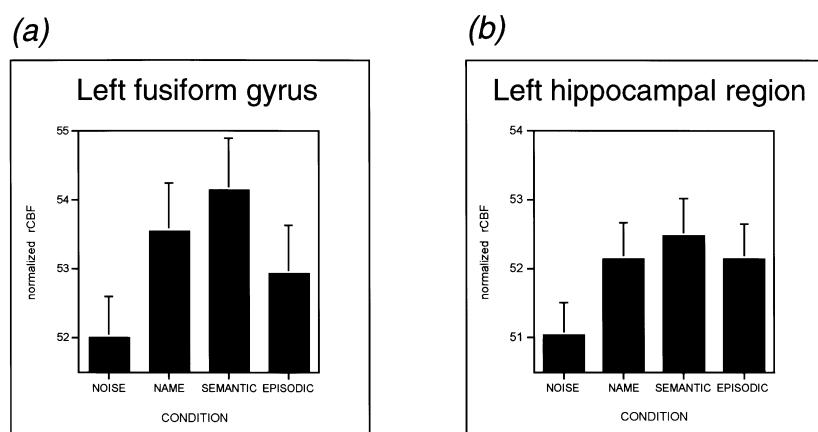


Fig. 3. Normalized rCBF values at the pixel of peak activity in (a) left fusiform gyrus (BA 20;  $-40, -32, -12$ ) and (b) left hippocampal region ( $-24, -36, 0$ ) during low level perceptual baseline (visual noise), object naming, semantic retrieval, and episodic retrieval.

Table 2

Local maxima within areas demonstrating significantly greater rCBF for the semantic and episodic retrieval conditions against a naming baseline

Brain regions (Brodmann area)	Coordinates			Z score
	x	y	z	
<b>Semantic retrieval greater than naming baseline</b>				
Frontal lobe				
L. middle frontal gyrus (9)	−39	16	28	4.34
R. middle frontal gyrus (9)	40	16	28	2.66
R. middle frontal gyrus (46)	28	46	8	2.61
Parietal lobe				
L. superior parietal cortex (7/19)	−32	−68	36	3.92
Temporal lobe				
L. fusiform gyrus (37)	−40	−38	−8	2.36
	−48	−48	−12	2.33
<b>Episodic retrieval greater than naming baseline</b>				
Frontal lobe				
R. middle frontal gyrus (9)	40	14	32	2.96
Parietal lobe				
L. superior parietal cortex (7/19)	−28	−68	32	6.17
L. posterior cingulate gyrus (23)/Retrosplenium	−4	−38	16	4.07
Precuneus (7)	0	−68	32	6.18
R. superior parietal cortex (7/19)	26	−72	32	4.44
R. posterior cingulate gyrus (23)/Retrosplenium	4	−34	16	3.88
R. thalamus (dorsomedial nucleus)	8	−18	4	3.29
Cerebellum				
L. cerebellum	−24	−50	−28	3.48
	−36	−62	−28	3.40
Midline cerebellum	0	−46	−24	3.34
	2	−60	−24	3.33

Notes: The coordinates are from the atlas of Talairach and Tournoux [74], where x, y, and z correspond to the right-left, anterior-posterior, and superior-inferior dimensions, respectively. Activations with  $Z \geq 3.09$  are reported (exceptions are italicized). Brodmann areas are included in parentheses.

that was centered in BA 8. A small area of increased activity in the right inferior frontal cortex (BA 11/47) was also found. In the left temporal cortex, a widespread area of increased activation extended along a ventral path from a posterior region ( $y = -44$ ) to a more anterior

( $y = -4$ ) region of the left inferior temporal gyrus (BA 37 and 20), including the parahippocampal gyrus. Less extensive areas of increased activation were found in the right fusiform gyrus (BA 20) and parahippocampal region (BA 36).



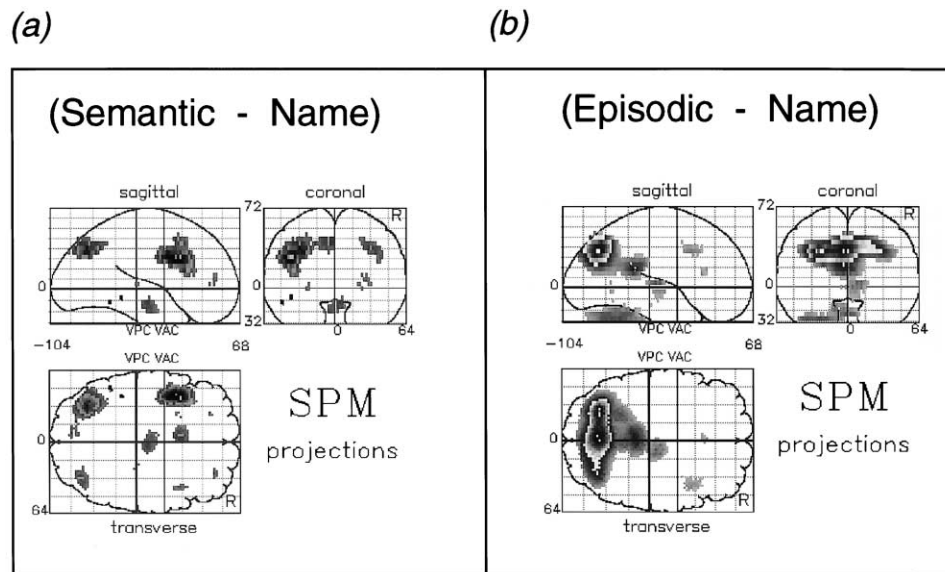


Fig. 4. Regions showing increased blood flow (thresholded to Z-scores  $\geq 2.33$ ) for (a) semantic and (b) episodic retrieval relative to the object naming baseline.

Table 3

Local maxima within areas demonstrating significantly greater rCBF for each of the retrieval conditions compared with each other

Brain regions (Brodmann area)	Coordinates			Z score
	x	y	z	
<b>Semantic retrieval greater than episodic memory</b>				
Frontal lobe				
L. superior frontal gyrus (8)	−12	26	44	5.20
L. inferior frontal gyrus (45)	−40	24	4	5.47
L. medial frontal gyrus (11)	−14	20	−12	4.52
L. medial frontal gyrus (10)	−10	40	−8	3.77
L. orbital frontal gyrus (11)	−20	44	−4	3.89
R. inferior frontal cortex (11/47)	26	28	−8	3.31
Temporal lobe				
L. inferior temporal gyrus (37)	−48	−44	−4	4.32
L. inferior temporal gyrus (20)	−42	−32	−8	4.09
L. fusiform/parahippocampal region (20/36)	−36	−20	−20	4.06
L. inferior temporal gyrus (20)	−36	−4	−24	4.30
R. fusiform gyrus (20)	40	−28	−20	3.23
R. parahippocampal region (36)	30	−12	−24	3.80
<b>Episodic retrieval greater than semantic memory</b>				
Anterior cingulate (24)	2	24	16	3.80
Parietal lobe				
Posterior cingulate gyrus (23)/Retrosplenium	0	−38	16	4.07
R. precuneus (7/31)	6	−64	36	6.64
R. thalamus (dorsomedial nucleus)	6	−14	4	3.41
R. brainstem	14	−38	−28	3.33
L. cerebellum	−24	−54	−28	3.64

Notes: The coordinates are from the atlas of Talairach and Tournoux [74], where x, y, and z correspond to the right-left, anterior-posterior, and superior-inferior dimensions, respectively. Only activations with  $Z \geq 3.09$  are reported. Brodmann areas are included in parentheses.

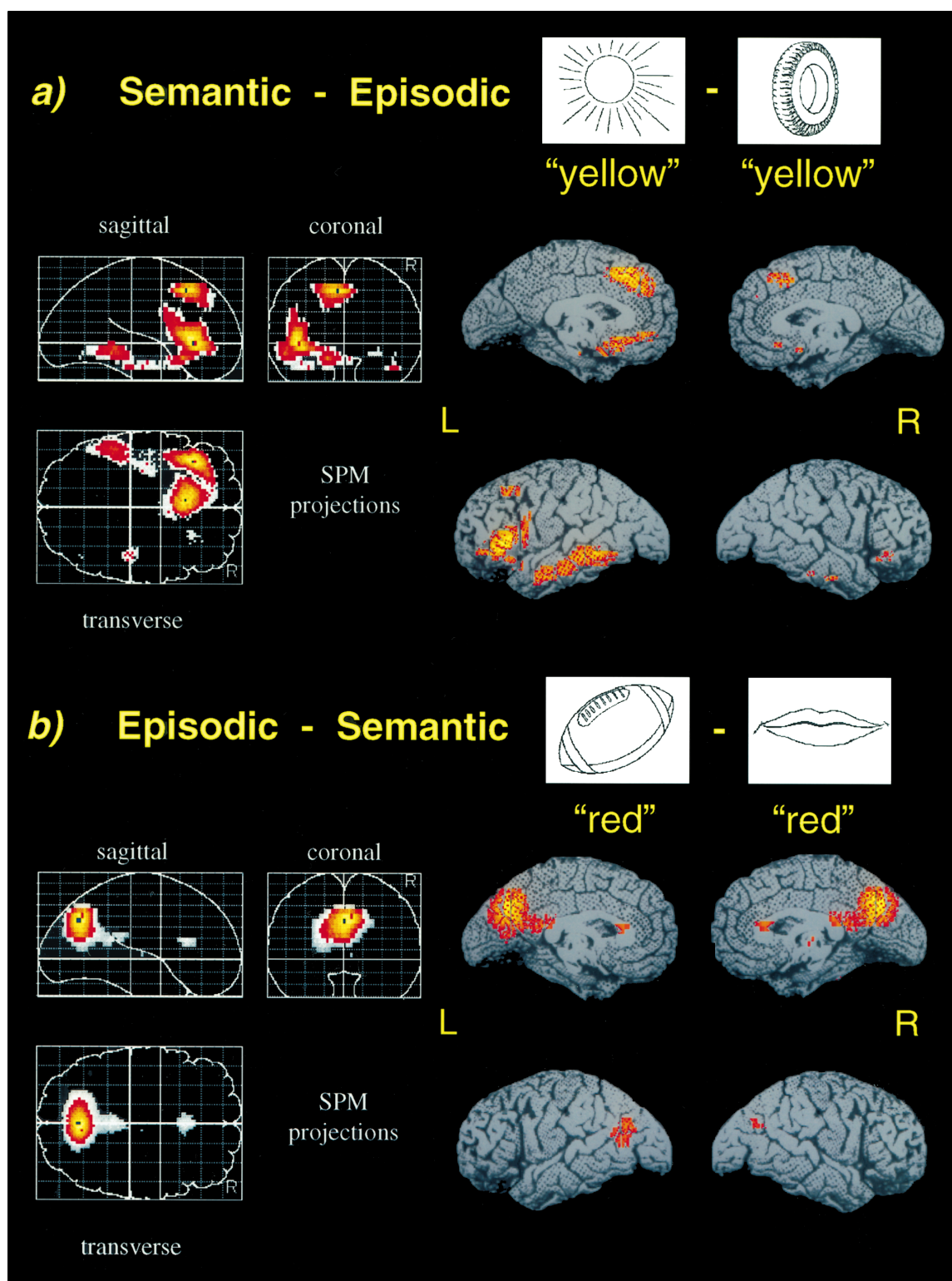


Fig. 5. Regions showing increased blood flow (thresholded to Z-scores  $\geq 3.09$ ) for (a) semantic retrieval relative to episodic retrieval and (b) episodic retrieval relative to semantic retrieval.

The more extensive activation in left temporal cortex revealed when semantic retrieval was compared with episodic retrieval (see Fig. 5a) than when compared with

naming (see Fig. 4a) suggested that episodic retrieval activated left temporal cortex less than did naming. This possibility was verified by an additional analysis that

showed greater activation along the left middle temporal gyrus ( $-50, -36, 0; z = 3.65$  and  $-42, +2, -12; z = 3.64$ ) for naming than episodic retrieval.

The main area of differential activation revealed in the episodic condition compared to the semantic condition was in medial parietal (BA 7/31) and retrosplenial cortices (see Fig. 5b). Additionally, smaller areas of increased activation were found in the anterior cingulate (BA 24), right thalamus, and left cerebellum.

As no activation was revealed in right frontal cortex for episodic relative to semantic retrieval, we investigated how rCBF was modulated in right frontal cortex across the three cognitive tasks. Two right frontal regions were selected: One was activated during both semantic and episodic retrieval relative to naming (BA 9;  $+40, +16, +28$ ), and one was selectively activated during semantic relative to episodic retrieval (BA 11/47;  $+26, +28, -8$ ). We submitted the rCBF values measured at these pixels to separate ANOVAs. The patterns of activation differed markedly across these regions (see Fig. 6). Both semantic and episodic retrieval produced notably higher rCBF values than naming in right BA 9 (Omnibus  $F(2, 30) = 3.6$ , with planned comparisons showing greater rCBF for semantic,  $F(1, 30) = 5.9$ , and episodic,  $F(1, 30) = 4.9$ , than for naming, all  $P$ 's  $< 0.05$ ; but no difference between semantic and episodic,  $P > 0.10$ ). In contrast, rCBF in right BA 11/47 was higher for naming and semantic retrieval than for episodic retrieval ( $F(2, 30) = 7.2$ , with planned comparisons showing greater rCBF for naming,  $F(1, 30) = 9.3$ , and semantic  $F(1, 30) = 12.0$ , than episodic, all  $P$ 's  $< 0.005$ ; but no difference between naming and semantic,  $P$ 's  $> 0.10$ ).

#### 4. Discussion

These results support the assertion that dissociable cortical systems subserve semantic and episodic memory. Whereas left temporal and left frontal cortices were acti-

vated most when subjects retrieved semantic information, the medial parietal region was activated most when retrieving episodic information. These results are consistent with findings from previous PET studies as discussed earlier. Despite our predictions, however, neither medial temporal nor right prefrontal cortices were selectively activated when subjects retrieved episodic information. Below we will discuss each of these brain regions in relation to our findings.

##### 4.1. Temporal lobes

All conditions, compared to a low level baseline, revealed bilateral activations of posterior temporal regions (greater on the left than right). This is consistent with lesion and functional imaging data suggesting that left posterior temporal cortex is the site for stored information needed to name an object [41, 43], to retrieve semantic information about an object [13, 40, 48, 67], or to retrieve episodic information about an object [35].

The degree to which the left temporal lobe was activated, however, varied according to what kind of information was retrieved. Specifically, retrieving semantic, but not episodic, information activated left ventral temporal cortex (BA 37) over and above naming. This same region was reported in our previous study [40] for the same semantic task contrasted with naming. In fact, the locations of maximum activity are practically identical (Martin et al. [40] report  $-46, -46, -12$  whereas the current study reports  $-48, -48, -12$  and  $-40, -38, -8$ ). The strength of the activations may have been weaker in the current study due to a slower stimulus presentation rate than that used in our initial study (see [55], for effects of presentation rate on degree of rCBF changes), to previous exposure to experimental materials in the current study (for reports of decreased blood flow in subjects shown re-presented stimuli, see [7, 39, 71]), or to the combined influence of both of these factors.

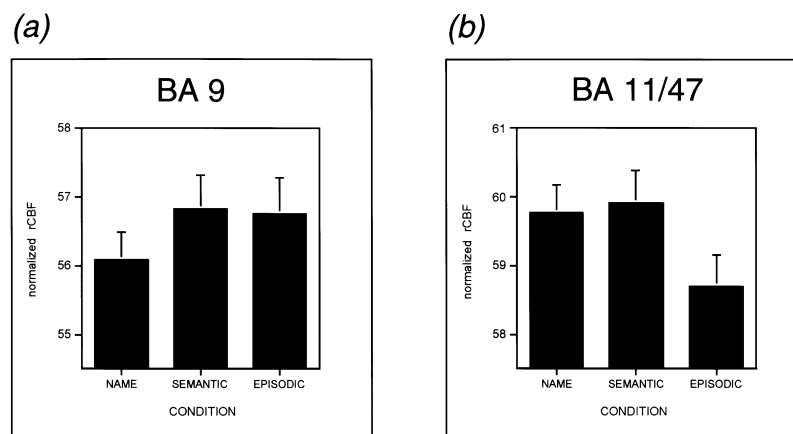


Fig. 6. Normalized rCBF values at the pixel of peak activity in right frontal cortex: (a) BA 9 ( $+40, +16, +28$ ) and (b) BA 11/47 ( $+26, +28, -8$ ) during naming, semantic retrieval, and episodic retrieval.

When episodic and semantic conditions were directly contrasted with each other, only the semantic condition revealed activation in left temporal cortex. Thus, although episodic memory about an object attribute is presumably stored in temporal cortex, our data suggest that retrieving a particular episodic memory associated with an object (i.e., a newly formed object-color association) does not recruit left temporal cortex to a greater extent than object naming. In fact, object naming produced more left temporal lobe activation than did the episodic retrieval task. Several explanations may address these results. One possibility is that recently learned information (in this case, a new color-object association) and highly over-learned material (in this case, an object's name and typical color) are both represented in left temporal cortex, but the representation of recently acquired information is weaker and more diffuse than the representation of over-learned information. As a result, the locus for storage of the newly formed (and likely soon to be forgotten) object-color association is not revealed when compared to over-learned, permanent semantic information, but can be seen relative to a low-level baseline task (staring at visual noise patterns). Alternatively, newly formed color-object associations may be stored focally, but not in the temporal lobes. The cortical areas most activated during episodic retrieval in the current study were the medial parietal and retrosplenial cortices, thus perhaps these regions constitute the locus for episodic memory storage.

#### 4.2. Medial parietal and retrosplenial regions

Retrieving episodic memories activated the medial aspect of the parietal lobe and the retrosplenial region to a greater extent than naming objects or retrieving semantic memories. These findings replicate several reports of selective activation of medial parietal cortex during episodic retrieval, as well as the differential involvement of medial parietal cortex in episodic retrieval relative to semantic tasks [16, 64]. These data are also in agreement with reports that damage to retrosplenial cortex [5, 80], as well as to adjacent medial parietal cortex [57], has resulted in amnesia, thus providing converging evidence that these regions are important for episodic memory function.

Do such findings suggest that these regions constitute the locus for episodic memories? Retrosplenial lesions, in particular, cause severe anterograde amnesia but relatively less retrograde amnesia [5], whereas temporal lobe lesions have been noted to cause retrograde amnesia for both semantic and episodic memories [e.g., 3, 35]. If remote memories are, indeed, stored in the retrosplenium, one would expect retrosplenial lesions to cause significant retrograde amnesia. Consistent with this possibility, Rudge and Warrington [57] reported profound retrograde amnesia in addition to anterograde amnesia in

patients whose lesions included medial parietal cortex. Under this framework, the medial parietal region was engaged in our study because subjects experienced extremely successful recovery of episodic information (their recall success rate was 97%), therefore reactivating stored information (see [33]).

However, it is more likely that the medial parietal region subserves a particular aspect of recovering episodic information (e.g., recapitulating the encoding event). One possibility, suggested by Fletcher and colleagues [15–17], is that the medial parietal region participates in imagery processes elicited to aid episodic retrieval. Specifically, they argue that medial parietal cortex is required for *inspecting* visual images (as opposed to regions associated with the automatic generation of images). The present data, however, do not support this hypothesis. Medial parietal cortex was activated during episodic retrieval, even when contrasted with a semantic task that would be expected to elicit a similar visual imagery process. In fact, post experimental interviews suggested that, in general, subjects were not aware of using imagery to a greater extent in the episodic condition than in the semantic condition.

Buckner and colleagues [8] also report contrary evidence for the visual imagery hypothesis; specifically, rCBF in the medial parietal region was no greater when subjects recalled a visual image (e.g., picture of a wheel) than when they recalled an auditorily presented word (e.g., “wheel”). Both episodic retrieval tasks activated medial parietal cortex. However, Buckner et al. reported two functionally dissociable areas within this region: A posterior area (−3, −72, +37) showing increased rCBF during episodic retrievals and an anterior area (−2, −53, +41) showing deactivations. Our data concur with these findings. Whereas we report episodic retrieval related activation in the medial parietal region relative to the visual noise baseline (+8, −76, +36) (see Table 1c), additional analyses showed that deactivations were found in a more anterior area of the medial parietal region (−2, −56, +40).

Such findings highlight the importance of identifying the specific brain pathways involved in episodic retrieval tasks. Given the extensive connections between medial temporal structures with medial parietal and retrosplenial regions [81], the role(s) of the medial parietal and retrosplenial regions is more consistent with the process of retrieval than storage of episodic memories.

#### 4.3. Medial temporal and diencephalic regions

Activations in the left medial temporal region were revealed for all conditions (naming, semantic retrieval, and episodic retrieval) when compared with a low level baseline (see Fig. 3b). Medial temporal activation during object naming is consistent with our previous report using the same low level baseline as the current study [42].

Moreover, detecting activation in the medial temporal region during episodic retrieval is consistent with other PET studies [52, 60, 61, 71]. The medial temporal region, however, was not selectively enhanced for episodic retrieval relative to naming or semantic retrieval [see also 1, 7, 8, 11, 16, 29, 34, 64, 79]. On the contrary, a greater activation of the left parahippocampal region was revealed when semantic retrieval was compared with episodic retrieval. This selective activation during semantic retrieval is in line with the assertion that the medial temporal region is part of a novelty assessment circuit [78], since the stimuli presented in the semantic condition were relatively more novel to subjects than were stimuli presented in the episodic condition. That is, in the context of this study, additional pre-exposure to the stimuli in the episodic condition made these stimuli more familiar relative to the stimuli in the semantic condition. Thus, in the current study, the medial temporal region was relatively more activated when processing less familiar stimuli.

Unlike our findings for the medial temporal region, episodic retrieval revealed significant thalamic activations, above that elicited by naming objects or by retrieving semantic information. This is in line with neuropsychological [10, 70] and functional imaging [8, 11, 16, 64] literature implicating the dorsomedial nucleus of the thalamus in episodic memory function.

#### 4.4. Frontal lobes

Retrieving semantic information recruited left frontal cortex to a greater degree than naming objects and retrieving episodic memories. This finding is in broad agreement with previous PET [23, 34, 40, 48, 54, 56, 83] and lesion data [32, 44] regarding semantic memory retrieval. The present data are also consistent with evidence from several imaging studies highlighting the participation of right frontal cortex during retrieval from episodic memory, regardless of whether the material is verbal [1, 7, 8, 11, 16, 26, 34, 52, 64, 77, 79] or nonverbal [2, 29]. Specifically, episodic retrieval recruited right prefrontal cortex over that required to simply name the objects. Moreover, consistent with predictions generated from the HERA model, rCBF was greater in left than right frontal regions during semantic memory retrieval, whereas rCBF was greater in right than left frontal regions during episodic memory retrieval. This latter assertion is due to the fact that the episodic condition did not produce any greater left frontal activity than that produced by object naming.

The current data, however, are not in complete agreement with predictions from the HERA model. Specifically, they are inconsistent with reports of greater activation in right frontal cortex when retrieving information from episodic than from semantic memory. Instead, we found similar levels of activity in frontal

cortex (BA 9) during retrieval from episodic and semantic memory above that recruited by naming. Moreover, semantic retrieval recruited an additional right frontal region (BA 46) that was not revealed in the episodic condition. Direct comparisons between the two retrieval tasks did not reveal greater activation in right frontal cortex during episodic retrieval, but in fact, revealed the opposite: contrary to predictions in line with the HERA model, right frontal cortex (BA 11/47) was activated more during semantic retrieval than episodic retrieval. In fact, episodic retrieval engaged this specific right frontal region the least of the three tasks (see Fig. 6).

The discrepancy between current and previous findings may be due to differences in the episodic tasks used. Specifically, the right frontal activation for the current episodic memory task may have been less robust than other reports because our task was less effortful (indicated by high accuracy scores and fast response times) than other episodic memory tasks reported. It has been proposed that frontal activation during retrieval is associated with the *attempt* to retrieve information from memory rather than the conscious recollection of the retrieved information [33, 52, 60]. Schacter et al. [60] suggest that retrieval attempt is related to the effort of retrieval and further, that blood flow in frontal regions is associated with that effort. Direct support for the association of right frontal activation and general effort is reported by Grady et al. [25], who found a linear increase in right frontal rCBF with increasing difficulty on a perceptual matching task.

Consistent with this argument, the more effortful “retrieval” tasks (semantic and episodic) selectively engaged right dorsolateral frontal cortex in BA 9 relative to naming. However, retrieval effort cannot explain the activations in all of right frontal cortex. In particular, the “semantic” tasks (naming objects and semantic retrieval) selectively engaged the more ventral region in BA 11/47 relative to episodic retrieval (see Fig. 6). Thus, although general effort could address the activation in BA 9 (supported by slower response times for both retrieval tasks than naming), it could not explain the activation in BA 11/47 (as subjects were faster at naming than either retrieval condition). The locations of these right frontal lobe activations are not anomalous, but have both been reported in previous episodic retrieval studies.

These distinct patterns of activation suggest that different regions within right frontal cortex may have specialized processing roles (cf [6]). For example, it may be that frontal lobe involvement varies according to the degree of strategic search demanded by the task (see [46]), or according to the degree of monitoring demanded by the task (see [58, 63, 64, 73]). Regardless, such evidence underscores the need to articulate what specific processes are involved in the effort of memory retrieval (semantic and episodic), and whether these processes are subserved by distinct regions within the frontal lobes.

#### 4.5. Cerebellum

Strong, bilateral activation of the cerebellum was found for all conditions relative to the low level baseline. These activations were expected, given the requirement to produce speech during the naming, semantic, and episodic retrieval tasks. In addition, episodic retrieval produced greater activation of the left cerebellum compared to object naming and to semantic retrieval (see [12] for studies showing left cerebellar activation for episodic retrieval). This finding was not due to effort, per se, as retrieval of color words was faster for the episodic condition than for the semantic condition. This finding is, however, consistent with the suggestion that the cerebellum plays a greater role in the initial acquisition and retrieval of newly acquired information (episodic condition) than in the retrieval of older, previously acquired, and well-established information (semantic condition) (see [38] for a recent discussion of the role of the cerebellum in learning).

#### 5. Summary

These results support the hypothesis that retrieving episodic and semantic memories recruit distinct neural areas, even though the tasks used in the current study were equated for accuracy, viewing conditions, and verbal responses. Consistent with predictions, we found that retrieving semantic information activated the left temporal and left frontal regions whereas retrieving episodic memories reliably activated medial parietal cortex, retrosplenial cortex, and thalamus. Our data deviated, however, from other predictions regarding neural correlates for episodic retrieval: Specifically, episodic retrieval recruited less left temporal cortex than naming objects and than retrieving semantic information, and recruited less right frontal cortex than retrieving semantic information. These findings suggest that temporal and right frontal regions are not obligatory components for all episodic retrieval.

#### Acknowledgements

We thank Susan Courtney, James Haxby, and Leslie Ungerleider for helpful discussions and their comments on the manuscript. We also thank the following people for their contributions: Peter Herscovitch, Richard Carson, Margaret Daube-Witherspoon, and Paul Baldwin for management and care of the NIH PET facility; Avi Karni for physician coverage; José Maisog for physician coverage, computer programming and assistance in data analysis; and Suzy Garber for assistance with task implementation. This work was performed at the National Institutes of Health.

#### References

- [1] Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Reza K, Watkins GL, Ponto LLB, Hichwa RD. Short-term and long-term verbal memory: A positron emission tomography study. *Proceedings of the National Academy of Sciences, U.S.A.* 1995;92:5111–5115.
- [2] Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Reza K, Watkins GL, Ponto LLB, Hichwa RD. Neural substrates of facial recognition. *Journal of Neuropsychiatry and Clinical Neurosciences* 1996;8:139–149.
- [3] Barr WB, Goldberg E, Wasserstein J, Novelly RA. Retrograde amnesia following unilateral temporal lobectomy. *Neuropsychologia* 1990;28:243–255.
- [4] Battig WF, Montague WE. Category norms for verbal items in 56 categories: A replication and extension of the Connecticut category norms. *Journal of Experimental Psychology Monograph* 1969;80:1–46.
- [5] Bowers D, Verfaellie M, Valenstein E, Heilman KM. Impaired acquisition of temporal information in retrosplenial amnesia. *Brain and Cognition* 1988;8:47–66.
- [6] Buckner RL. Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychonomic Bulletin and Review* 1996;3:149–158.
- [7] Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME. Functional anatomical studies of explicit and implicit memory retrieval tasks. *Journal of Neuroscience* 1995;15:12–29.
- [8] Buckner RL, Raichle ME, Miezin FM, Petersen SE. Functional anatomic studies of memory retrieval for auditory words and visual pictures. *Journal of Neuroscience* 1996;16:6219–6235.
- [9] Buckner RL, Tulving E. Neuroimaging studies of memory: Theory and recent PET results. In *Handbook of Neuropsychology* Vol. 10, ed. F. Boller and J. Grafman. Elsevier, Amsterdam, 1995, pp. 439–466.
- [10] Butters N, Stuss DT. Diencephalic amnesia. In *Handbook of Neuropsychology* Vol. 3, ed. F. Boller and J. Grafman. Elsevier, Amsterdam, 1989, p. 107–148.
- [11] Cabeza R, Kapur S, Craik FIM, McIntosh AR, Houle S, Tulving E. Functional neuroanatomy of recall and recognition: A PET study of episodic memory. *Journal of Cognitive Neuroscience* 1997;9:254–265.
- [12] Cabeza R, Nyberg L. Imaging cognition: An empirical review of PET studies with normal subjects. *Journal of Cognitive Neuroscience* 1997;9:1–26.
- [13] Demonet, J.-F., Chollet F, Ramsay S, Cardebat D, Nespoulous, J.-L., Wise R, Rascol A, Frackowiak R. The anatomy of phonological and semantic processing in normal subjects. *Brain* 1992;115:1753–1768.
- [14] De Renzi E, Liotti M, Nichelli P. Semantic amnesia with preservation of autobiographical memory: A case report. *Cortex* 1987;23:575–597.
- [15] Fletcher PC, Frith CD, Baker SC, Shallice T, Frackowiak RSJ, Dolan RJ. The mind's eye: Precuneus activation in memory-related imagery. *Neuroimage* 1995;2:195–200.
- [16] Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RSJ, Dolan RJ. Brain systems for encoding and retrieval of auditory-verbal memory: An in vivo study in humans. *Brain* 1995;118:401–416.
- [17] Fletcher PC, Shallice T, Frith CD, Frackowiak RSJ, Dolan RJ. Imagery and semantic cueing in episodic memory: The influence of imagery and semantic cueing. *Brain* 1996;119:1587–1596.
- [18] Fox PT, Mintun MA. Noninvasive functional brain mapping by charge-distribution analysis of average PET images of H215O. *Journal of Nuclear Medicine* 1989;30:141–149.
- [19] Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: The assessment of significant change.

- Journal of Cerebral Blood Flow and Metabolism 1991;11:690–699.
- [20] Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Plastic transformation of PET images. *Journal of Computer Assisted Tomography* 1991;15:634–639.
  - [21] Friston KJ, Frith CD, Liddle PF, Lammertsma AA, Dolan RJ, Frackowiak RSJ. The relationship between local and global changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism* 1990;10:458–466.
  - [22] Friston KJ, Passingham RE, Nutt JG, Heather JD, Sawle GV, Frackowiak RSJ. Localization in PET images: Direct fitting of the intercommissural (AC–PC) line. *Journal of Cerebral Blood Flow and Metabolism* 1989;9:690–695.
  - [23] Frith C, Friston K, Liddle P, Frackowiak R. A PET study of word finding. *Neuropsychologia* 1991;29:1137–1148.
  - [24] Gabrieli JDE, Brewer JB, Desmond JE, Glover GH. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 1997;276:264–266.
  - [25] Grady CL, Horwitz B, Pietrini P, Mentis MJ, Ungerleider LG, Rapoport SI, Haxby JV. The effect of task difficulty on cerebral blood flow during perceptual matching of faces. *Human Brain Mapping* 1996;4:227–239.
  - [26] Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ. Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain* 1993;116:1–20.
  - [27] Grober E, Sliwinski M. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology* 1991;13:933–949.
  - [28] Hart J Jr, Gordon B. Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. *Annals of Neurology* 1990;27:226–231.
  - [29] Haxby JV, Ungerleider LG, Horowitz B, Maisog JM, Rapoport SI, Grady CL. Face encoding and recognition. *Proceedings of the National Academy of Sciences, U.S.A.* 1996;93:922–927.
  - [30] Herscovitch P, Markham J, Raichle ME. Brain blood flow measured with intravenous O-15 water: I. Theory and error analysis. *Journal of Nuclear Medicine* 1983;24:782–789.
  - [31] Hurtig RR, Hichwa RD, O'Leary DS, Boles Ponto LL, Narayana S, Watkins GL, Andreasen NC. Effects of timing and duration of cognitive activation in [<sup>15</sup>O] water PET studies. *Journal of Cerebral Blood Flow and Metabolism* 1994;14:423–430.
  - [32] Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR. Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behavioral Neuroscience* 1989;103:548–560.
  - [33] Kapur S, Craik FIM, Jones C, Brown GM, Houle S, Tulving E. Functional role of the frontal cortex in retrieval of memories: A PET study. *Neuroreport* 1995;6:1880–1884.
  - [34] Kapur S, Craik FIM, Tulving E, Wilson AA, Houle S, Brown GM. Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proceedings of the National Academy of Science U.S.A.* 1994;91:2008–2011.
  - [35] Kapur N, Ellison D, Smith MP, McLellan DL, Burrows EH. Focal retrograde amnesia following bilateral temporal lobe pathology. *Brain* 1992;115:73–85.
  - [36] Kucera H, Francis WN. Computational analysis of present-day American English. Brown University Press, Providence, RI, 1967.
  - [37] Lee KS, Berger KL, Mintun MA. Mathematical registration of PET images enhances detection of neural activation foci by subtraction image analysis. *Journal of Cerebral Blood Flow and Metabolism* 1991, 11 (Suppl. 2), S557.
  - [38] Leiner HC, Leiner AL, Dow RS. The underestimated cerebellum. *Human Brain Mapping* 1995;2:244–254.
  - [39] Martin A, Lalonde FM, Wiggs CL, Weisberg J, Ungerleider LG, Haxby JV. Repeated presentation of objects reduces activity in ventral occipitotemporal cortex: A fMRI study of repetition priming. *Society for Neuroscience Abstracts* 1995;21:1497.
  - [40] Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG. Discrete cortical regions associated with knowledge of color and knowledge of action. *Science* 1995;270:102–105.
  - [41] Martin A, Wiggs CL, Ungerleider LG, Haxby JV. Neural correlates of category specific knowledge. *Nature* 1996;379:649–652.
  - [42] Martin A, Wiggs CL, Weisberg J. Modulation of human medial temporal lobe activity by form, meaning, and experience. *Hippocampus* 1997;7:587–593.
  - [43] McCarthy RA, Warrington EK. Visual associative agnosia: A clinico-anatomical study of a single case. *Journal of Neurology, Neurosurgery and Psychiatry* 1986;49:1233–1240.
  - [44] Milner B. Some cognitive effects of frontal-lobe lesions in man. *Philosophical Transactions of the Royal Society of London B* 1982;298:211–226.
  - [45] Minoshima S, Berger KL, Lee KS, Mintun MA. An automated method for rotational correction and centering of three-dimensional functional brain images. *Journal of Nuclear Medicine* 1992;33:1579–1585.
  - [46] Moscovitch M. Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience* 1992;4:257–267.
  - [47] Moscovitch M, Kapur S, Kohler S, Houle S. Distinct neural correlates of visual long-term memory for spatial location and object identity: A positron emission tomography study in humans. *Proceedings of the National Academy of Sciences, U.S.A.* 1995;92:3721–3725.
  - [48] Mummery CJ, Patterson K, Hodges JR, Wise RJS. Generating 'tiger' as an animal name or a word beginning with T: Differences in brain activation. *Proceedings of the Royal Society of London B* 1996;263:989–995.
  - [49] Nelder JA, Mead R. A simplex method for function minimization. *Computer Journal* 1965;7:308–313.
  - [50] Nyberg L, Cabeza R, Tulving E. PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review* 1996;3:135–148.
  - [51] Nyberg L, McIntosh AR, Houle S, Nilsson L-G, Tulving E. Activation of medial temporal structures during episodic memory retrieval. *Nature* 1996;380:715–717.
  - [52] Nyberg L, Tulving E, Habib R, Nilsson LG, Kapur S, Houle S, Cabeza R, McIntosh AR. Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* 1995;7:249–252.
  - [53] Parkin AJ, Leng NRC. *Neuropsychology of the Amnesic Syndrome*. Lawrence Erlbaum, Hillsdale, 1993.
  - [54] Petersen SE, Fox PT, Posner MI, Mintun MA, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single word processing. *Nature* 1988;331:585–589.
  - [55] Price CJ, Moore CJ, Frackowiak RSJ. The effect of varying stimulus rate and duration on brain activity during reading. *Neuroimage* 1996;3:40–52.
  - [56] Raichle ME, Fiez JA, Videen TO, MacLeod AMK, Pardo JV, Fox PT, Petersen SE. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex* 1994;4:8–26.
  - [57] Rudge P, Warrington EK. Selective impairment of memory and visual perception in splenic tumours. *Brain* 1991;114:349–360.
  - [58] Rugg MD, Fletcher PC, Frith CD, Frackowiak RSJ, Dolan RJ. Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* 1996;119:2073–2083.
  - [59] Sakai K, Miyashita Y. Memory and imagery in the temporal lobe. *Current Opinion in Neurobiology* 1993;3:166–170.
  - [60] Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS. Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proceedings of the National Academy of Sciences, U.S.A.* 1996;93:321–325.
  - [61] Schacter DL, Reiman E, Curran T, Yun LS, Bandy D, McDermott KB, Roediger H L III. Neuroanatomical correlates of veridical

- and illusory recognition memory: Evidence from positron emission tomography. *Neuron* 1996;17:267–274.
- [62] Schacter DL, Tulving E. What are the memory systems of 1994? In *Memory Systems 1994* ed. D. L. Schacter and E. Tulving. MIT Press, Cambridge, 1994, pp. 1–38.
- [63] Shallice T. From neuropsychology to mental structure. Cambridge University Press, Cambridge, 1988.
- [64] Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RSJ, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature* 1994;368:633–635.
- [65] Shimamura AP. Memory and frontal lobe function. In *The Cognitive Neurosciences* ed. M. Gazzaniga. MIT Press, Cambridge, 1995, pp. 803–813.
- [66] Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: Norms for naming agreement, familiarity, and visual complexity. *Journal of Experimental Psychology (Human Learning)* 1980;6:174–215.
- [67] Snowden JS, Goulding PJ, Neary D. Semantic dementia: A form of circumscribed cerebral atrophy. *Behavioral Neurology* 1989;2:167–182.
- [68] Snowden JS, Griffiths H, Neary D. Semantic dementia: Autobiographical contribution to preservation of meaning. *Cognitive Neuropsychology* 1994;11:265–288.
- [69] Squire LR. Memory and forgetting: Long-term and gradual changes in memory storage. In *Selectionism and the Brain: International Review of Neurobiology* Vol. 37, ed. Sporns O, Tononi G. Academic Press, San Diego, 1994, pp. 243–69.
- [70] Squire LR, Amaral DG, Zola-Morgan S, Kritchevsky M, Press G. Description of brain injury in the amnesic patient N. A. based on magnetic resonance imaging. *Experimental Neurology* 1989;105:23–35.
- [71] Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences, U.S.A.* 1992;89:1837–1841.
- [72] Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR. The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences, U.S.A.* 1996;93:8660–8665.
- [73] Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, Pogue J. Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. *Neuropsychology* 1994;8:355–373.
- [74] Talairach J, Tournoux P. *Co-planar Stereotactic Atlas of the Human Brain*. Thieme, Stuttgart, 1988.
- [75] Tulving E. Episodic and semantic memory. In *Organization of memory* ed. E. Tulving and W. Donaldson. Academic Press, New York, 1972, pp. 381–403.
- [76] Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Sciences, U.S.A.* 1994;91:2016–2020.
- [77] Tulving E, Kapur S, Markowitsch HJ, Craik FIM, Habib R, Houle S. Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition. *Proceedings of the National Academy of Sciences, U.S.A.* 1994;91:2012–2015.
- [78] Tulving E, Markowitsch HJ, Craik FIM, Habib R, Houle S. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex* 1996;6:71–79.
- [79] Tulving E, Markowitsch HJ, Kapur S, Habib R, Houle S. Novelty encoding networks in the human brain: Positron emission tomography data. *Neuroreport* 1994;5:2525–2528.
- [80] Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT. Retrosplenial amnesia. *Brain* 1987;110:1631–1646.
- [81] Van Hoesen GW. The parahippocampal gyrus: New observations regarding its cortical connections in the monkey. *Trends in Neuroscience* 1982;5:345–350.
- [82] Wheeler MA, Stuss DT, Tulving E. Towards a theory of episodic memory: The frontal lobes and autonoetic consciousness. *Psychological Bulletin* 1997;121:331–354.
- [83] Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 1991;114:1803–1817.